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DIETARY IMPACT ON THE GUT MICROBIOME AND ITS EFFECTS ON CLOSTRIDIUM DIFFICILE, INFLAMMATORY BOWEL DISEASES, AND METABOLIC SYNDROMES

(Review Article)

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Abstract

Gut microbiomes have long been known to have diverse effects on normal human health. Medical researchers and microbiologists have studied how it is maintained, about its composition, and how it can be altered. Different types of diets have varied implications on the gut microbiota and its homeostasis. This review paper discusses the different studies conducted on the matters of how diets influence the gut microbiome and also its effect on certain medical conditions, Clostridium difficile infection, Inflammatory bowel disease, and metabolic syndrome.

Diet and its effects on the gut microbiome and how it impacts human health

The diet is the source of the microbiome's fuel. But the diet also seeds the microbiota. The fascinating aspect of the role of diet in the microbiome is that some research has shown that it is almost 5 times more important than the genetics of the host [50]. So, what we eat is 5 times more important in terms of microbiome and health effects than the genes we were given at birth.

Usually, short term diet modifications are temporary [50]. Long-term diet changes can dramatically alter the composition of the microbiota [39,50]. A microbiota that is more complex benefits from a more diverse diet. The only widely recognized marker of a balanced microbiome is the more complex microbiome [48].

With the human host, the microbiome has a symbiotic relationship [9]. Around 15% of the carbohydrates we consume go to the microbiota of the intestine. And that's mostly what we'd only consider fiber-a microbiome power [5]. The gut also contains a very small amount of fat and 5-34% protein. There is a reduction in diversity if we increase our caloric intake while retaining the carbohydrates, protein, and fat proportions [11,50]. In general, indicators of detrimental effects on the microbiome are known to be a subsequent rise in firmicutes and a decrease in bacteroidetes [11]. There would be an increase in diversity if there were a reduction in calorie consumption while keeping the same diet [11].

Fiber and Short Chain Fatty Acids

In the upper part of the digestive tract, macro and micronutrient absorption take place. The lower part is where the microbiome is in the digestive tract. They harvest energy from foods we wouldn't be able to consume otherwise [45]. And that raises our energy needs by up to 10 percent and that is mainly the digestion of fiber. They contain short-chain-fatty-acids such as butyrate, acetate, and propionate when they digest fiber [27]. Fiber is a dietary bulk-forming factor and is essential for regularity. And that's controlled by intestinal transit time. We decrease the intestinal transit period when we take a high fiber diet. This contributes to an increase in short-chain-fatty-acid production [27]. Interestingly, increased short-chain-fatty-acid development improves motility, which then decreases the time of intestinal transit. So, to keep the system normal, we now have a constructive feedback loop. Another side effect is that the pH is also decreased, which may help to absorb some nutrients, such as iron.

The positive feedback loop contributes to a rise in the prevalence of butyrate-producing bacteria, which is one of the short-chain-fatty acids that are safe. It also contributes to a reduction in the incidence of pathogenic bacteria and the commensals are spared. So, above all, healthy bacteria can flourish.

Fats and Proteins

In a high fiber diet, what we see is just the reverse: a decline in diversity and a reduction in a healthy microbiome. It is possible to see an improvement in the microbiome that thrives off fat and protein, rather than fiber. This suggests that short-chain-fatty-acids are decreasing. The healthy fat in a

high-fat diet can be productive [44]. The diversity of the microbiome is not lost if the diet is high in healthy fats.

Micronutrients

Nutrients are formed in the microbiome. There are also B vitamins that come from our microbiome. Since a large proportion comes from the gut microbiota, the stocks of these vitamins in the body are greater than we can expect from consuming food [51]. Interestingly enough, one of the major risk factors is SIBO- Small Intestinal Bowel Overgrowth linked to the microbiome [26]. Thiamine is synthesized and made in higher stores by the microbiome and contributes to the nutritional status. If the good microbiome is eliminated from the body, adequate thiamine will not be produced by the body [18]. For the microbiome, vitamin B6 is important because they need it for their enzymatic activities and so our diet depends on their vitamin B6 diet. Research has shown the possible relationship between how virulent and how basic H. Pylori and its capacity to make B6 are going around [11]. It becomes more virulent and more modal if it can supply its B6, which is potentially harmful to a patient.

The amount of folate that the microbiome produces is considerable. In the production of folate, resistant starch is indeed essential. If the body does not have enough resistant starch in the diet, a significant amount of folate is possibly not developed by the intestinal microbiome [18].

There is also vitamin B12 provided by the gut microbiome. But it's still important for the microbiome's metabolism. They depend on a Vitamin B12 diet. It has everything to do with our epigenetics and maybe the relationship between the host and the microbiome in an epigenomic fashion. In one study, vitamin B12 was shown to require 83 percent of the gut microbiota. So, if the diet does not supply the gut microbiota with adequate vitamin B12, they are likely to die [18,51].

As an electron carrier, the microbiota uses vitamin K, and thus supplying vitamin K via diet is essential for microbiota sustenance [12]. It is proven that beta carotene can be produced by the microbiome. But the human body requires retinol, the activated form. And we haven't shown that retinol activates bacterial beta carotene yet. Besides, no evidence exists as to whether they contribute to vitamin A status. Between the microbiota, in modern Western babies, B. infantis are found to be largely absent. Supplementing B. Infantis cures all conditions pretty much because it is strongly anti-inflammatory and removes autoimmune disorders, asthma, atopic dermatitis. But the impact of B. Infantis depends on providing enough vitamin A. Supplementing B. Infantis, thus, does little for a child with vitamin A deficiency [20].

As they don't have a vitamin D receptor, vitamin D is not important to the microbiome. But for the immune system, vitamin D is essential and the way our immune system responds to commensal bacteria depends on vitamin D [10].

Iron is not well explored, in large part. What is known from the research is that there appears to be a shortage of Lactobacilli in iron-deficient patients [51]. The directionality of the Iron-Lactobacilli relationship is not well known. We recognize, however, that Lactobacilli requires iron. An iron-deficient patient wouldn't provide the gut microbiome with enough iron. There were no supplementation trials, however, showing that supplementing with iron would boost this.

Polyphenols

A lot of health benefits have been related to polyphenols. The body mainly does not absorb polyphenols. 90 percent of them make it to the large intestine, where the gut microbiome is likely to bioactivate them [51]. So, many of the polyphenols' effects may be attributable to their effects on the microbiome and through it. To find out the role of polyphenols in red wine and the effect of alcohol, a scientific study was carried out. It was carried out by the distribution of de-alkalized wine and pure alcohol. The result showed an improvement in microbiota and the wine as a whole meal showed a substantial increase. Synergistic, it was. The effect of the wine and the effect of the alcohol added together did not, however, match the effect of the wine as a whole. The effect of bringing them together was far greater [51].

Clostridium difficile infection

As shown above, diet influences the human gut through different means, which then also affects human health conditions [19]. Clostridium difficile, an anaerobic bacteria through the exotoxins,

TcdA and TcdB produced by them are accountable for the c.difficileinfections (CDI) worldwide. In murine model studies conducted for CDI, associations between antibiotic consumption and intestinal microbiome are noted along with non-antibiotic disruption of the gut microbiome [41]. The human gut microbiome resists the invasion of pathogenic bacterias through colonization resistance mechanisms of competing with harmful invasive species [46]. The bacteriocin produced by the species B.thuringiensis has shown efficacy in inhibiting the growth of, particularly spore-forming Clostridium difficile [34].

There have been indications that multiple unexplored environmental factors, like nutrients, and host factors probably impact CDI through various mechanisms. Because diets containing high amounts of carbohydrates are used for the survival of different bacterial species, we can hypothesize the role diets can play a vital role in the gut microbiome regulation and hence influences CDI. Several studies have demonstrated that diet can alter and manipulate the gut's microbiome make-up and its functions [54].

Most of the research on CDI is done on murine models so as to understand the mechanisms of nutrient component breakdowns, and detect bacterial involvement, and manipulate different gut colonization. Studies on mice have shown traditional diets to be fermentable food, mainly wheat and other starches which are mainly composed of fructooligosaccharides (FOS). Although not digested by mammals, anaerobic bacterial species like clostridium and lactobacillus can ferment them by cleaving their bonds. This is suggestive of inhabitant gut microbes to thrive and promotes resistance to the pathogenic invasion of c.difficile [32]. Contrary to traditional diets, defined diets consist of mainly “non-fermentable” fibers, and carbohydrates that are easily metabolized. The contents of these defined diets are absorbed relatively easily by the GI tracts of mammals [32]. In another study directed at the more common higher fat-protein diet, and carbohydrate richer diet, the results showed that the higher carbohydrate diet was readily metabolized to monosaccharides and although they encourage the colonization of c.difficile they also mitigate the overgrowth. Additionally, results revealed that despite the type of carbohydrate, a low protein-fat and a relatively higher carbohydrate diet was preventative to a certain extent [30]. The same study also showed mice undertaking antibiotic treatment for CDI, low protein diets showed resident gut bacterias competing with invasive pathogenic clostridium species for amino acids thereby helping combat CDI in the presence of antibiotic use [30].

Zinc also has a significant role in the modulation of the gut microbiota. Higher levels of zinc is seen to aggravate the severity of CDI and worsen conditions. Adversely, lesser quantities of zinc in the diets of the patients with CDI or those at risk of developing CDI have displayed protective effects. Calprotectin, a protein complex that participates in the sequestering of zinc, has antimicrobial properties against Clostridium difficile making it a significant element of the innate immune response to CDI. By restricting the availability of Zinc, calprotectin helps in confronting c.difficile [52,53].

Symptomatic relief for CDI patients can also be achieved by adding probiotics to their diet. Imbalances in the gut microbiota caused by antibiotic treatment frequently tend to exacerbate diarrhea and vomiting, symptoms mediated by toxins produced by c.difficile. The use of probiotics in CDI patients remarkably decreased the relapse of the infection and also proved to decrease the number of diarrheal episodes post-antibiotic treatment [13].

Inflammatory bowel diseases

As we have seen in the case of Clostridium difficile infections, diet also tends to play an immense role in inflammatory bowel disease (IBD). IBD is a general term for Crohn'sdisease (CD) and ulcerative colitis (UC), which are chronic inflammatory disorders of the gastrointestinal (GI) tract. Over the years, there has seen an increase in incidence all over the world and can be said as a global disease even [3]. Like several other illnesses, IBD is also multifactorial. The ultimate cause of the conditions is still unclear, but several studies conducted thus far have suggested both immune dysregulation and dysbiosis as the probable factors for the inflammations. There is limited evidence on IBD onset and genetic influences on how they correlate, considering all the developments in genetics over the years [21]. The Crohn's and Colitis Foundation is currently undertaking numerous projects to concentrate on preclinical IBD mechanisms, including genetic and microbiome-based mechanisms. Among the priorities to be assessed, environmental stimuli, primarily the diet are included.

Influence of diet on the Etiopathogenesis of Inflammatory bowel disease

In recent reviews of various literature on IBD, the most ubiquitous environmental factor found in IBD was diet. In all regional settings, diet is either a protective or a risk factor in both, UC and CD. It must certainly be the most ubiquitous environmental factor in IBD patients, taking into account the fact that all patients with IBDs are exposed to food and diet also affects the gut microbiota, which is significant in all IBD patients [8]. It is well known that gut microbiota presence is imperative for gut inflammation and additionally it is also known that diet plays a crucial role in its formation. Over the years several different types of approaches were made to understand the part diet plays in IBD, reviewing these data, we can observe that there were noticeable risk factors based on individual diets.

High consumption of plant-based fibers showed a low risk of CD, whereas a deficiency in zinc in CD patients was noted in a cohort study of IBD patients [1]. Dietary fibers tend to be fermentable and make them easier to be metabolized by the gut microbiome into short-chain fatty acids which can inhibit NFκβ and the transcription of pro-inflammatory markers [1]. Zinc however plays role in intestinal epithelial cell integrity mainly through the delocalization of E-cadherin and β–catenin in intestinal epithelial cells and also in an inhibitory effect on NFκβ which is associated with inflammation and also reduction of myeloperoxidase activity, the latter mechanism was noted in animal models of IBDs [1]. High potassium and high sodium diets have also been established as having anti-inflammatory through their effects on inducing Foxp3 and on TH17 cells, which also on cohort data analysis showed inverse effects on IBD [23]. The dietary modification that causes a disparity in the fatty acid levels and also improves the permeability also tends to sulfur production which can manipulate the gut microbiota to grow more sulfate-reducing bacterias like firmicutes [22].

Curative effect diet may have on inflammatory bowel disease

The objectives for the treatment of IBD are to promote and sustain remission, decrease the need for long-term use of anti-inflammatory medications, enhance the quality of life and improve the prognosis. Anti-inflammatory agents are the cornerstones of the current treatment. In approximately 30 percent of patients who undergo surgical interventions, the procedures may result in a pouch or end ileostomy, although they are curative for UC [36]. None of these surgical choices are without complications and pouchitis will occur in up to 70 percent of patients with a pouch [14]. With more than 80% of patients needing surgical resection, an even higher number of CD patients require surgery, which is not even completely effective [36]. During the course of further understanding IBD and finding different approaches to manage and treat IBD, diets have become studied and researched to a greater extent. Various components of our diet play vital roles in bringing a balance to the gut microbiome, which is most important for IBD.

Diet as a therapy for IBD must be taken into consideration with multiple studies showcasing the differences associated with increased and decreased risk of IBD. Studies have shown that animal fat and protein-rich diets compared to plant-based fiber-rich diets have a higher risk of IBD. As mentioned above the plant-based diet has protective factors that are helpful for the gut microbiome to induce anti-inflammatory functions of cells by metabolizing the nutrients into short-chain fatty acids [28]. A plant-based diet also blocks bacterial translocation across the Peyer's patches, which prevents invasion of certain bacterias which contributes to some of the pathogenesis of IBD [35].

Exclusive enteral nutrition is used as a supplemental treatment for IBD patients. Phytonutrients and phytochemicals are sometimes added to some of the formulas because they have shown positive results in controlling inflammation. Xanthohumol and curcumin have both demonstrated inhibition of COX, LOX, suppress TNFα, and downregulate NF-κB activation which is beneficial for IBD patients [37]. An anti-inflammatory diet (IBD-AID) for IBD has shown positive results [33]. The IBD-AID emphasizes on modification of certain carbohydrates because they provide a substrate for bacterias to proliferate, consumptions of pre and probiotic foods to rejuvenate the lost gut microbiota, and differentiating between fats which are beneficial for treating IBD [33]. Probiotic consumption can induce remission according to studies conducted on bacterial secretion butyric acid, which showed significant effects on cellular proliferation and apoptosis. It also has anti-inflammatory properties and helps in the strengthening of mucosal barriers, which are both supportive in IBD treatment [47]. Butyrate-producing bacteria are found

to be promising therapeutic probiotic bacterial strains [47]. Lastly, certain probiotics raise the levels of vitamin D, which influences the gut by maintaining gut homeostasis, improving epithelial cell's integrity, immune responses, and also the composition of the gut microbiome [6]. Vitamin D is beneficial in treatment especially because multiple immune cell types express Vitamin D receptors (VDR) and it has been evidenced through murine model studies that VDR deficiency increases the risk for developing colitis [17].

Metabolic syndrome

As mentioned in the sections above, we know that diet influences the physiology and metabolism of the host by interacting with the gut microbiota [43]. Current evidence has shown that gut microbiota is altered in people with obesity, type 2 diabetes, and stroke. This indicates that the gut microbiota could be a significant environmental factor leading to the progression of metabolic diseases. Dietary interventions are also a possible method for modulating intestinal microbiota and further impacting the health of the host.

A decrease in consumption of indigestible carbohydrates may result in the loss of certain bacteria residing in the human gut, which depends on these sources and thereby decreases the production of short-chain fatty acids [40]. The connection between dietary fiber and the incidence of type 2 diabetes, and dietary fiber and whole grains has shown the increased diversity of the microbiota of the human gut. High fiber intake is associated with the increased levels of the bacterial genus Prevotella.

A study performed by Kovatcheva-Datchary et al observed that changes in postprandial glucose and insulin response following a 3-day barley kernel bread intervention are based on the enrichment of P. copri in the participant's microbiota. This was functionally related to improved efficiency in digesting complex polysaccharides in the barley kernel bread. In those with no improvement in glucose metabolism after the intervention, it was observed that their gut microbiota was neither enriched with P. copri nor their ability to ferment complex polysaccharides improved after the trial. These results suggest that gut microbiota analysis could be used to understand how each individual responds to the dietary intervention [24].

Bile acid is an endocrine molecule, which in addition to the absorption of fat-soluble nutrients, also regulates numerous metabolic processes, including glucose, lipid, and energy balance [31]. Through the direct or indirect activation of a nuclear receptor, bile acids play a role in the metabolism of glucose and lipids: Farnesol X (FXR) and a membrane receptor: G protein-coupled membrane receptor 5. (TGR5). When natural bile acids are supplied as FXR activators, the metabolism of gut microorganisms can produce TGR5 ligands. The gut microbiota induces the inflammation of adipocytes by increasing the expression of genes involved in the absorption of lipids in the liver. The microbial community interacts dynamically with bile acids. This interaction may have positive or negative effects on host metabolism through dietary changes [38,42]. Increasingly, the gastrointestinal tract's metabolic ability and its microbiota are regarded as promising goals for developing glycaemic regulation and managing type 2 diabetes. More specifically, recent data have shown that the glucose-lowering effects of metformin are influenced by improvements in gut microbiota composition and function [16].

Several gut-targeting treatment strategies to reduce blood sugar are emerging and promising initially, but there is a need to better understand the mechanisms that underlie these effects in humans.

Dyslipidemia and atherosclerotic plaque remain a significant risk factor for cardiovascular disease and is often closely linked to impaired glucose metabolism and obesity [29]. In reducing the effects of long-standing dyslipidemia short-chain fatty acids (SCFAs) have a potentially promising therapeutic role [4]. The human gut lacks the enzymatic ability to break down certain foods, including complex carbohydrates as dietary fiber. But certain anaerobic bacteria present in the large intestine ferment these fibers into many by-products like SCFAs. By activating the free fatty acid receptor (FFAR) 2 coupled with G proteins, SCFAs induce the activation of the gut hormones peptide YY (PYY) and glucagon-like peptide-1 (GLP-1). Among SCFAs, propionate shows the greatest affinity for FFAR 2.

A randomized, cross-over study was conducted to determine the effects of propionate on appetite regulation. Propionate has been shown to stimulate the gut release of the PYY and GLP-1, leading to a reduction in energy consumption in humans. A decrease in weight gain, intra-abdominal adipose tissue,

and hepatic fat distribution, and prevented the decline in insulin sensitivity was seen in the subject group after 24 weeks of propionate supplementation [7]. Optimizing the development of colonic propionate by choosing propionate rich dietary fibers may be a new way of preventing lifelong weight gain and improving health status.

To evaluate the preventive effects of different types of fiber like lupin kernel, legume, and citrus on cardiovascular disease, a randomized crossover study was performed [15]. Subjects on high-fiber diets (i.e., lupin or citrus fiber) underwent a reduction in C-reactive protein, systolic blood pressure, and blood lipid circulation. The authors proposed that the hypolipidemic effects of a fiber-rich diet were due to the production of SCFA. Although SCFAs can have significant tropic effects on the body and health while LPS and peptidoglycan, the components of the bacterial cell wall can contribute to cardiovascular disease risk [2]. For example, LPS-injected mice showed decreased HDL cholesterol in plasma and elevated plasma triglycerides [49]. A retrospective human study of 587 people in the Finnish Diabetic Neuropathy cohort showed that those with the highest serum LPS levels also had substantially higher serum triglyceride and blood pressure levels [25]. Microbial components can also present a risk for metabolic syndrome.

Conclusion and future perspective

In conclusion, we recognize that the abundance of researches and literature on how diet impacts the human gut microbiome has opened up new possibilities to approach not only in treating Clostridium difficile, Inflammatory bowel disease, and metabolic syndrome but also in understanding how it is associated with the conditions itself. Significant associations of the gutmicrobiome with host metabolism, inflammatory, endocrine, and immune homeostasis, and suspected gut microbiome upregulation or alteration have shown to be enormous. In effect, the disturbance of such a fragile equilibrium would contribute to the disease's manifestation. However, owing to a lack of direct evidence and mechanistic information, the causal or association relationship remains debatable. Our knowledge of the gut microbiome is still at a very preliminary level, to better explain the relation, with many weaknesses and research holes worth further exploration. In addition, the commensal microbial composition will impact the host factors' growth, maturation, and normal functioning in turn. A better understanding of the human microbiota and how commensal microbes communicate with the host is certainly relevant in order to elucidate the pathophysiology and metabolic aspects of many human diseases and to provide a more efficient therapeutic framework to tackle the limitations of existing therapies. In short, there is still a relatively new but rapidly growing area of research in the Human Microbiome, showing many preliminary but encouraging studies on the modulatory role of the human microbiome in human well-being and disease. Future applications for the detection of microbiome-based diseases, monitoring of prognosis, prophylaxis, and therapies that have great potential to revolutionize existing disease prevention and treatment measures are certainly worth anticipating. More research is warranted on how diet can be used as an adjunct therapy for these conditions and given the multiple effects diet has on not only the gut microbiome but also on human immune responses studies can also be made on unearthing prevalence of various conditions due to dietary modifications.

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